REMARKS

Claims 28-34 are pending. No new matter has been added by way of the present amendment. For instance, non-elected claims 19-23 are cancelled herein without prejudice to a disclaimer of the subject matter contained therein. Additionally, claims 24-27 and 35-38 are cancelled herein without prejudice to our disclaimer of the subject matter contained therein. Accordingly, no new matter has been added.

In view of the following remarks, Applicant respectfully requests that the Examiner withdraw all rejections and allow the currently pending claims.

Issues under 35 U.S.C. §103(a)

The Examiner has rejected claims 21-29 and 32-36 under 35 U.S.C. §103(a) as being obvious over Nakagawa et al., USP 5,142,647 (hereinafter referred to as Nakagawa '647) in view of JP 07-133225 (hereinafter referred to as JP '225). Applicant respectfully traverses this rejection.

As a preliminary matter, Applicant points out that claims 24-27, 35 and 36 are cancelled herein. Accordingly, the rejection with respect to these cancelled claims is moot. Only claims 28, 29, 32, 33 and 34 remain pending and are under rejection over Nakagawa '647 in view of JP '225.

The Present Invention and Its Advantages

Independent claim 28 relates to a method of evaluating the effect of a medicine against asthenopia, which comprises the steps of: (1) (a) stimulating a ciliary muscle derived from a

non-human test animal with a chemical stimulant to induce a first contraction of said ciliary muscle, and washing said ciliary muscle at a point where the contraction reaches a plateau; and (b) repeating step (a) 3 to 50 times and terminating at a point where said ciliary muscle shows a decrease of 50 $\pm$ 20% in the tension of muscle contraction, thereby producing *in vitro* asthenopia of the ciliary muscle; (2) contacting said ciliary muscle with a medicine in the presence of said chemical stimulant; and (3) comparing the decrease in the tension of the muscular contraction before and after contact with the medicine.

Thus, the present invention is directed to a method for evaluating the effect of a medicine against asthenopia. Asthenopia refers to a pathological symptom often caused by fatigue of the ciliary muscle. This can be generated by prolonged or intense use of the eyes (see section of "Eye Strain" in "*Medical Dictionary*" 2nd Ed., p. 236, Oxford, New York, Oxford University Press (1998), copy submitted with the Reply of January 5, 2005). Also, to date no effective medicine for treating asthenopia has been developed except for chondroitin sulfate or sodium hyaluronate.

The lack of effective medicines is due to the previous lack of an experimental model for appropriately evaluating asthenopia. Thus, prior to the present invention there has been no means for appropriately screening a medicine which exhibits curative effects for asthenopia. However, as a result of the present inventor's various studies, it was found that repetition (for example, 3 to 50 times or more) of the following steps: (1) administering an inducer of muscular contraction (for example, acetylcholine) to contract the muscle; and subsequently (2) washing to remove the inducer, can lessen the tension of ciliary-muscle contraction. This generates a fatigued ciliary muscle (i.e., a ciliary muscle of which tension of muscular contraction is

decreased to 50 ± 20%), which can be used as an evaluation system for medicines for curing asthenopia.

In other words, in the experimental model of the present invention, since the ciliary muscle is fatigued, and the tension of muscular contraction is decreased to, for example, 50 ± 20%, administration of a medicine to the experimental model and measurement of tension recovery of the muscular contraction of ciliary muscle enables evaluation of the therapeutic effects of the medicine on asthenopia.

Prior to the present invention there has been no report on the fact that repetitive steps of contraction of a ciliary muscle and washing generate a fatigued ciliary muscle and also enable evaluation of a medicine for curing asthenopia.

Distinctions Between the Present Invention and the Cited References

In the outstanding Office Action the Examiner has referred to a Magnus apparatus as disclosed by Nakagawa '647. However, the present invention provides a method for screening a therapeutic medicine against asthenopia using a Magnus or other apparatus. Nakagawa '647 never discloses a method for evaluating such medicine, as admitted by the Examiner. Based on this alone, the present invention would not be easily expected from Nakagawa '647.

The Examiner has attempted to cure the deficiencies of Nakagawa '647 with the disclosure of JP '225. However, as can be seen from the following Table, the present invention is clearly different from JP '225.

Table

	JP '225	Present Invention
Material	Ciliary muscle exhibiting normal tension of muscular contraction	Ciliary muscle exhibiting normal tension of muscular contraction
Steps	-	Treatment of the above-mentioned ciliary muscle with an inducer of muscular contraction (e.g., acetylcholine), to induce a first muscular contraction
	-	Repetition of the treatment with the inducer of muscular contraction 3 to 50 times, to give a ciliary muscle of which tension of muscular contraction is decreased to 50 * 20% of a normal value
	Treatment of a ciliary muscle exhibiting normal tension of muscular contraction with a compound to be tested (Compound A)	Treatment of a ciliary muscle of which tension of muscular contraction is decreased with a compound to be tested in the presence of an inducer of muscular contraction (e.g., acetylcholine)
	-	Comparison of the degree of contraction of the ciliary muscle before and after treatment with the compound to be tested
	Subsequent treatment of the ciliary muscle with KCl (inducer of muscular contraction)	-
Effects	Evaluation of a suppression effect of contraction by the compound to be tested on muscular contraction of a ciliary muscle which is generally induced by KCl (an inducer of muscular contraction)	Evaluation of a recovery effect of muscular contraction by the compound to be tested on a ciliary muscle of which tension of muscular contraction is decreased

A review of the above Table reveals that the present invention clearly differs from JP '225. These differences relate to actual limitations required by the present claims as well as the effects of the present invention. For instance, Applicant highlights the following distinctions.

First, while ciliary muscle exhibiting normal muscle contraction is used "as is" for evaluation of a medicine in JP '225, ciliary muscle of which the tension of muscular contraction is decreased to 50 ± 20% (i.e., fatigue ciliary muscle) is used for evaluation of a medicine in the present invention.

Second, JP '225 is a method for evaluating the suppression effect of contraction by a medicine (antagonism of a medicine against KCl) on ciliary muscle which generally contracts with an inducer of muscular contraction (KCl). In this method of JP '225, a recovery effect of muscular contraction of a ciliary muscle of which tension of muscular contraction was lost cannot be evaluated. On the other hand, the present invention is a method for directly evaluating the recovery effect of muscular contraction by a medicine for a fatigue ciliary muscle of which tension of contraction is decreased.

Third, while the same fatigued ciliary muscle can be repeatedly used to evaluate therapeutic effects of multiple medicines in the present invention, the ciliary muscle cannot be used in such embodiment in JP '225.

Based upon the above, Applicant respectfully submits that even if one of ordinary skill in the art were motivated to combine the references of Nakagawa '647 and JP '225, the present invention could not be achieved. This is due to the fact that several limitations according to the present claims are completely absent from the prior art. Accordingly, there exists no *prima facie*

case of obviousness. Reconsideration and withdrawal of this rejection are therefore respectfully requested.

The Examiner has also rejected claims 30, 31, 37 and 38 under 35 U.S.C. §103(a) as being obvious over Nakagawa '647 in view of JP '225 as applied to claims 24-29 and 32-36 above and further in view of JP '225 in view of Kitagawa (Japanese Journal of Pharmacology, 1989, Vol. 49, suppl. pp. 281 (hereinafter referred to as Kitagawa). Applicant respectfully traverses this rejection.

As a preliminary matter, Applicant points out that claims 37 and 38 are cancelled herein. Accordingly, only claims 30 and 31 remain under rejection.

Distinctions between the present invention and Nakagawa '647 and JP '225 were discussed above. Kitagawa simply discusses smooth muscle contraction by acetylcholine as a stimulatory agent. Thus, Kitagawa fails to address any of the deficiencies with respect to Nakagawa '647 and JP '225 discussed above. Accordingly, this rejection is overcome for the same reasons as discussed above. Reconsideration and withdrawal thereof are respectfully requested.

In view of the above, Applicants respectfully submit that the present claims define allowable subject matter. Accordingly, the Examiner is respectfully requested to withdraw all rejections and allow the currently pending claims.

If the Examiner has any questions or comments, please contact Craig A. McRobbie, Registration No 42,874 at the offices of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for

any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated: August 3, 2006

Respectfully submitted,

By #42,874

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